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Continuous positive airway pressure by face mask or mechanical ventilation in patients with human immunodeficiency virus infection and severe *Pneumocystis carinii* pneumonia

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Abstract. We reviewed the records of 44 patients with AIDS who had 45 episodes of severe *Pneumocystis carinii* pneumonia (PCP). While 9 patients required intubation and mechanical ventilation (MV) on admission, continuous positive airway pressure (CPAP) by face mask was the initial measure in 36 episodes. There were 25 patients managed with CPAP alone, 23 of whom survived. Among the reasons for delayed intubation and MV (11 patients) was that treatment failure was strongly associated with non-survival, since all 6 such patients died. The in-hospital mortality for severe PCP in this study was 33% overall, and reached 65% for mechanically ventilated patients. The 1-year survival was 43% (95% confidence interval, 28%–58%). These data confirm the improved prognosis for patients with AIDS and severe PCP, and suggest that mask CPAP may be an adequate mean of ventilatory support in this setting.

Key words: Acquired immunodeficiency syndrome – *Pneumocystis carinii* pneumonia – Respiratory insufficiency – Positive end expiratory pressure – Critical care – Steroids

Pneumocystis carinii pneumonia (PCP) remains the most common life-threatening opportunistic infection in patients with AIDS, occurring in 70%–80% of such patients during the course of their illness [1–3]. In severe PCP, respiratory failure requiring mechanical ventilation (MV) has been associated with poor survival, with in-hospital mortality rates as high as 86%–94% in early studies [4–6], and persisting in the range of 48%–66% in recent reports [7–11].

Continuous positive airway pressure (CPAP) was first employed in the management of the respiratory distress syndrome of the newborn (12), and has later been proposed in patients with both hemodynamic and non-hemodynamic pulmonary edema [13, 14] or post-extubation hypoxemia following major surgery [15]. Although some authors cite CPAP as an alternative to MV in respiratory failure due to PCP [16–18], few studies report in detail the outcome of such patients [10, 19]. In the ICU of Bichat-Claude Bernard hospital, in an attempt to avoid intubation and MV, we often employ CPAP in HIV-infected patients with acute respiratory failure due to severe PCP.

This study was conducted in order to characterize patients with AIDS and severe PCP admitted to our ICU according to their modalities of ventilatory support, either CPAP by face mask or mechanical ventilation.

Methods

Patients

Charts of all patients with HIV infection and severe PCP admitted to the intensive care unit (ICU) of Bichat-Claude Bernard hospital from November 1986 to January 1989 were reviewed retrospectively.

The severity of acute illness on admission was assessed with the simplified acute physiology score [20].

The diagnosis of PCP was made in all patients by silver methenamine staining of bronchoalveolar lavage (BAL) fluid obtained by bronchoscopy. The severity of PCP on admission to the ICU was assessed by the presence of signs of marked respiratory distress, an arterial oxygen pressure (PaO_2) below 55 mmHg with the patient breathing room air and the need for positive pressure ventilation, either CPAP by face mask or mechanical ventilation.

Mask CPAP was administered on admission in the absence of hypercapnia and when patient's cooperation was adequate. The apparatus used included a continuous gas flow system, a reservoir bag, a cascade humidifier, a silastic face mask tightly adjusted with head straps and a threshold resistor PEEP valve. We began with 40 l/min flow, 100% oxygen and 5 cm H_2O PEEP. We adjusted gas flow according to patient's ventilatory demand. The level of PEEP was then increased in 2–3 cm H_2O steps until F_IO_2 could be lowered to 60%. When the patient's condition improved, we progressively weaned CPAP by 2–3 cm H_2O decrements over a few days; CPAP was then progressively replaced by high flow nasal oxygen.

Intubation and MV were performed on admission when inadequate patient's co-operation or hypercapnia precluded the use of CPAP. Later in the ICU course, the change from mask CPAP to MV was justified by post-operative care after open-lung biopsy, evidence of deterioration following bronchoscopy or treatment failure; the latter was defined by persistence of signs of respiratory failure despite CPAP with up to 12 cm H_2O PEEP or MV after 5–7 days of therapy.

Evidence of other infections was recorded, either at the time of the diagnosis of PCP or during the clinical course. Cytomegalovirus (CMV) infection was diagnosed when characteristic cytopathic effects were seen in open-lung biopsy specimen or at autopsy. In addition, viral cultures of BAL specimens were routinely studied by indirect immunofluorescence with specific monoclonal antibodies; when CMV early antigen was detected in rapid culture, CMV co-infection was judged possible and was taken into account according to the preference of the treating physician. Nosocomial pneumonia was defined as the occurrence or persistence of fever (temperature over 38 °C), purulent sputum or tracheal aspirate associated with a new and persistent infiltrate on chest radiograph and the culture of at least 10^3 cfu/l from a protected specimen brush obtained by bronchoscopy [21]. Catheter-related infection was defined as the presence of at least 10^3 cfu on culture of the distal catheter segment [22]. Urinary tract infection was defined by the culture of at least 10^5 organisms/ml urine. Primary bacteremia was defined as the culture of any organism from blood culture, unrelated to an identified primary focus. Secondary bacteremia was considered with each primary septic focus.

Non-survivors of the acute episode of PCP were defined as patients who died either in the ICU or after discharge from the ICU, but without leaving the hospital. The follow-up period for survivors after hospital discharge ranged from 1–50 months.

Statistical analysis

Quantitative data are expressed as mean ± SEM. The means of groups were compared by a one-way analysis of variance (ANOVA); when a difference was detected, a multiple comparisons analysis was performed using Fisher's PLSD method. X^2 analysis was used for percentages; when the expected numbers were below 5, groups were combined appropriately in order to improve the accuracy of the test; Yate's correction was employed when necessary. $p < 0.05$ was considered significant. A Kaplan-Meier survival curve was used to estimate long-term survival in patients who were discharged from the hospital. Confidence limits were calculated using Greenwood's formula.

Results

There were 46 documented episodes of severe PCP in 45 patients with HIV infection during the study period. One patient was excluded because he also had severe chronic obstructive pulmonary disease. The mean age of the remaining 44 patients was 37.5 ± 2.9 years. 40 of them were male. The risk factor for HIV infection was male homosexuality or bisexuality in 30 patients, intravenous drug abuse in 7, history of blood transfusion in 2, and undetermined in 5. PCP was the first opportunistic infection in 33 episodes (73%). Three patients received zidovudine prior to the ICU admission. Four episodes were relapses of PCP.

The 45 episodes of PCP were divided into 4 groups:

- group I: episodes managed with mask CPAP alone ($n = 25$);
- group II: patients requiring MV on admission ($n = 9$);
- group III: patients initially managed with mask CPAP, and requiring delayed MV because of treatment failure (IIIa, $n = 6$) or other reasons (IIIb, $n = 5$), including deterioration following BAL (3 patients) or postoperative care after open-lung biopsy (2 patients).

The only patient who suffered 2 episodes of severe PCP during the study period (within a 10-month interval) was managed twice with CPAP alone, and was discharged from the hospital.

Data assessing the severity of patients on admission are shown in Table 1. Although a trend toward a difference was seen for group II patients, especially for PaO_2, the 4 groups did not differ significantly overall. The initial PaO_2 on room air for the overall episodes was 37.9 ± 1.1 mmHg. Although our patients had high serum LDH and evidence of BAL neutrophilia, no difference could be detected between groups.

Table 2 shows the modalities of ventilatory support in the 4 groups of patients. In group I patients, CPAP was administered for an average duration of a week, with relatively low levels of PEEP. Among group III patients, who were intubated after 8.2 ± 2.2 days of mask CPAP, treatment failure was associated with a longer duration of MV.

Intravenous trimethoprim-sulfamethoxazole was the initial therapeutic regimen in 42 episodes of PCP. The full course of this medication was completed in 25 episodes (56%); in 17 (38%), a switch to pentamidine and/or difluoromethylornithine was necessary because of

Table 1. Initial severity of disease

	CPAP only	MV on admission	Delayed MV	
			Treatment failure	Other
Group	I	II	IIIa	IIIb
No. of episodes	25	9	6	5
SAPS[a]	9.8 ± 0.6	11.7 ± 1.0	10.8 ± 0.8	7.8 ± 1.6
PaO_2[b] (mmHg)	39.5 ± 1.4	33.3 ± 2.0	41.8 ± 3.3	40.4 ± 4.1
Serum LDH[c] (U/L)	1395 ± 188 (n[d] = 17)	1892 ± 319 ($n = 5$)	1331 ± 332 ($n = 4$)	1164 ± 443 ($n = 3$)
BAL[e] neutrophilia (%)	14.6 ± 2.8 ($n = 15$)	28.6 ± 11.5 ($n = 5$)	36.5 ± 15.5 ($n = 3$)	9.5 ± 2.5 ($n = 4$)

[a] Simplified acute physiology score
[b] While breathing room air
[c] Lactate dehydrogenase
[d] Number of episodes with data available
[e] Bronchoalveolar lavage

Table 2. Ventilatory support

	CPAP only	MV on admission	Delayed MV	
			Treatment failure	Other
Group	I	II	IIIa	IIIb
No. of episodes	25	9	6	5
Duration (days)	6.9±1.6[a]	20.7±3.8	24.8±6.7[b]	13.2±4.4
PEEP (cmH_2O)	6.4±0.8[c]	10.3±1.1	11.5±0.5	10.8±2.7

[a] $p<0.01$ vs group II and IIIa
[b] $p<0.05$ vs group IIIb
[c] $p<0.01$ vs every other group

toxicity (8 episodes) or treatment failure (9 episodes). Systemic corticosteroids were administered in all episodes of PCP, 3.4±0.5 days after specific antimicrobial therapy was initiated; in 16 of 46 episodes (35%), steroids were given more than 3 days after treatment was begun. In 34 episodes (73%), steroid therapy consisted of intravenous methylprednisolone, 240 mg daily for 3 days followed by 120 mg for 3 days and 60 mg for 3 days. In the remaining 12 episodes, methylprednisolone was administered according to the preference of the treating physician, usually 2–4 mg/kg daily for a few days followed by a tapering regimen over 7–10 days.

In 4 episodes (9%), a concomitant opportunistic infection was diagnosed during the ICU course, including esophageal candidiasis, CMV retinitis, cryptococcosis and Salmonella infection. In addition, CMV pulmonary co-infection was judged possible (on the basis of BAL immunofluorescence data) in 8 patients, and was proven in 4 additional patients (by open-lung biopsy); 2 of these 4 patients recovered after antiviral therapy was given. Bacterial nosocomial infections occurred in 15 patients. In 12 of them, nosocomial infections were diagnosed at the time they were mechanically ventilated, and included nosocomial pneumonia ($n = 4$), catheter-related infection ($n = 5$), urinary tract infection ($n = 6$) and primary bacteremia ($n = 2$). Nosocomial infections during CPAP ventilation consisted in primary bacteremia ($n = 2$) and pulmonary infarction superinfection ($n = 1$). Pneumothorax occurred during MV in 6 patients, while none was observed in patients ventilated by mask CPAP.

Short-term mortality data are given in Table 3. The overall in-hospital mortality for severe PCP was 33%. The need for MV at any time during the ICU course was

Table 3. In-hospital mortality

	CPAP only	MV on admission	Delayed MV	
			Treatment failure	Other
Group	I	II	IIIa	IIIb
No. of episodes	25	9	6	5
Died	2 (8)	6 (67)	6 (100)	1 (20)
ICU	0	4	5	1
ward	2	2	1	0

Numbers in parentheses represent percentages

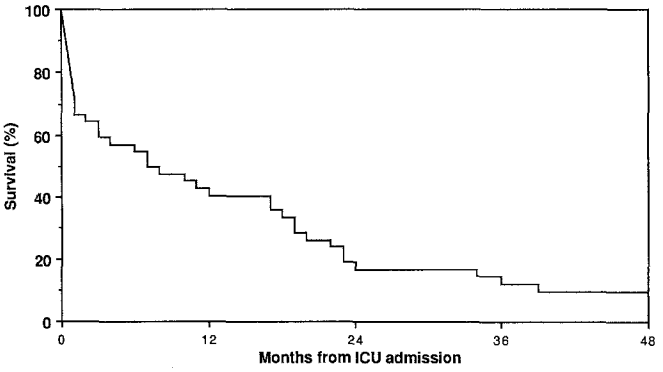

Fig. 1. Kaplan-Meier survival curve from time of ICU admission for patients with severe *Pneumocystis carinii* pneumonia

strongly associated with death, since 13 of these 20 patients died, vs 2 of 25 group I patients ($p<0.001$). Among the 10 patients who died in the ICU, death was due to uncontrolled respiratory failure in 8 patients 3 of whom had severe bronchopleural fistula. In addition, 3 of these 8 patients had evidence of nosocomial pneumonia at the time of demise. The 2 remaining patients died in the ICU of septic shock (related to primary bacteremia) and acute obstruction of the endotracheal tube, respectively. Postmortem lung histology was available in 10 patients, showing pulmonary fibrosis ($n = 7$), residual *P. carinii* infection ($n = 6$) and/or CMV pneumonia ($n = 5$). Among the 5 patients who died after discharge from the ICU (but without leaving the hospital), the reason for demise was massive pulmonary embolism ($n = 1$), wasting syndrome ($n = 2$), or unknown ($n = 2$).

A Kaplan-Meier survival curve of the patients from the time of ICU admission is provided in Fig. 1. The 1-year survival was 43% (95% confidence interval [CI], 28%–58%). The 2-year survival was 19% (95% CI, 7%–31%).

Discussion

This study describes the features of 45 episodes of severe PCP, according to the modalities of ventilatory support. While 9 unco-operative patients with profound hypoxemia required emergency intubation on admission, CPAP by face mask was the initial measure in 36 episodes of severe PCP; despite severe hypoxemia, 25 (69%) of such patients recovered and were discharged from the hospital. This 31% in-hospital mortality rate is lower than expected, since it corresponds to the risk of death of patients with a PaO_2 on room air at admission averaging 60 mmHg [23]. If we consider the overall 46 episodes, mortality reaches 33% for a mean PaO_2 of 38 mmHg. There are numbers of potential reasons for the improved short-term prognosis in these patients.

First, it may be due to recent improvements in therapy of PCP. However, new therapies such as difluoromethylornithine were seldom employed, and only 3 patients received zidovudine prior to the ICU admission. As part of an open study, all our patients were administered high dose steroids; in 35%, steroids were given more than 3 days after specific antipneumocystis therapy. This treat-

ment has recently been proven of benefit in patients with moderate-to-severe PCP [24, 25]. In patients with severe PCP, steroids given as "salvage" or "rescue" therapy (i.e., more than 72 h after specific therapy was begun) did not seem to improve survival [26]. However, a benefit could have been demonstrated with a more important sample size and/or higher dosages of steroids. On the basis of these data, a beneficial effect of steroids in this study cannot be excluded.

Second, high AIDS experience may have influenced mortality. Bichat-Claude Bernard hospital is a 1014 acute-care bed university hospital with a high level of experience with AIDS. The medical ICU of the Infectious Diseases Department is composed of 18 beds and admits 400–500 patients per year, 30%–35% of whom are infected with HIV.

According to Bennett et al., this high AIDS familiarity may contribute to lower the in-hospital mortality for patients with PCP [27].

Finally, the frequent use of CPAP in our institution may have influenced mortality. The 64% mortality rate for mechanically ventilated patients in this study is in agreement with the 60% and 66% rates reported in two institutions where CPAP is often employed in the management of severe PCP [10,11]. Together with the rather lower rates (48%–50%) reported elsewhere for such patients [8, 9], these data suggest that initial response to CPAP by mask may identify a less acutely ill subset of patients, and avoids intubation and MV in some of them. The complications of MV are well documented, and often contribute to the fatal outcome in ICU patients [28]. In this study, complications such as barotrauma, airway obstruction and nosocomial infection occurred mainly in mechanically ventilated patients and contributed to or were responsible for death in at least 5 patients. On the contrary, few complications were observed in patients managed with CPAP by face mask. Although this obviously reflects differences in severity of underlying disease, the low complication rate observed with CPAP may have contributed to the improved outcome.

When delayed MV is required in patients managed with CPAP, the reason for intubation is of considerable prognostical importance. Deterioration following bronchoscopy is related to an acute but transient hypoxemia [29], and carries a rather good prognosis [7, 16]. In this study, 4 of 5 patients who required intubation following BAL or after an open-lung biopsy survived. On the contrary, the 6 patients in whom worsening oxygenation and treatment failure led to MV died in the hospital. No parameter, including initial PaO_2, could predict treatment failure in these patients. However, this could reflect inadequate sample size. These data are in good agreement with a recent study that reports a 100% mortality rate for comparable patients [19]. In the report from Friedman et al. [10], the reasons for switching from CPAP to MV are not clearly stated; however, their overall results seem less pessimistic, since 5 of 8 such patients survived. In the setting of respiratory failure due to PCP, when no improvement is observed after 5–7 days of conventional therapy, a fortiori when progressive deterioration of oxygenation occurs, the main diagnostic hypothesis should include early fibrosis, microbiological failure and an associated infection, especially CMV [30]. Lung histology data in this study suggest that pulmonary fibrosis (despite high-dose steroids) and persistent *P. carinii* infection (despite changes in antimicrobial therapy) are often responsible for treatment failure. Moreover, 5 of 10 patients had histological evidence of CMV infection at autopsy. In mild PCP, CMV does not seem to affect mortality [31, 32]. However, when severe respiratory failure develops in the setting of PCP, this virus may represent an additional cause of lung injury, particularly when high dose steroids are administered [33]. In this study, patients in whom CMV early antigen was detected in BAL rapid culture were considered to be at risk of CMV infection, and were administered antiviral therapy when their respiratory status did not improve or deteriorated on conventional treatment. However, this attitude is of unproven benefit and should not be proposed routinely for patients with PCP.

This study documents a 1-year survival of 43% in patients with HIV infection and severe PCP. This contrasts markedly with previous studies where 1-year survival was less than 10% [5, 6, 11], but is in agreement with the 37% survival rate recently reported for patients managed either with CPAP or MV [34].

To summarize, our study confirms the overall better prognosis of patients with AIDS and severe PCP. CPAP by face mask is a safe and effective mean of ventilatory support in this setting, and probably avoids intubation in some patients. When mechanical ventilation is required, mortality remains high, particularly in patients who continued to deteriorate despite CPAP and maximal antimicrobial therapy.

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